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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,664	08/17/2001	Denise L. Faustman	DLF-002.1P	4530

7590 01/10/2007

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	PAPER NUMBER
1657	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
2 MONTHS	01/10/2007	PAPER

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/913,664
Filing Date: August 17, 2001
Appellant(s): FAUSTMAN, DENISE L.

Denise L. Faustman

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 10/10/2006 appealing from the Office action mailed 9/14/2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,081,030	CIVIN	1-1992
5,670,358	LEE et al	9-1997
6,156,306	BROWLEE et al	12-2000

Galati et al. "Quantitative cytometry of MHC class I digestion from living cells". Cytometry. (1997), vol. 27, pp. 77-83.

Stone et al. "Porcine cartilage transplants in the cynomolgus monkey". Transplantation. (1998), vol. 65, no. 12, pp.1577-1583.

Abbas et al. Cellular and Molecular Immunology. 5th edition (2003), pages 78-80.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,081,030 (Civin).

Claims are directed to a method for inhibiting rejection by a host mammal of another mammal donor tissue wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen, step of transplanting the treated viable donor tissue into host mammal before MHC are re-expressed and step maintaining the treated viable donor tissue in the host mammal. Some claims are further drawn to donor and host

mammals belonging to the same species. Some claims are further drawn to the use of tissue cells such as blood cells, precursor cell, bone marrow cells.

US 5,081,030 discloses a method for transplantation bone marrow cells wherein the method comprises step of treating a viable donor tissue with enzyme chymopapain (col. 11, lines 30-35), step of transplanting the treated viable donor tissue into host mammal (col. 11, line 45) and step maintaining the treated viable donor tissue in the host mammal (col. 11, line 57). The cited patent clearly teaches that the cells retain viability after enzymatic treatment. Both donor and host are rats or mammals belonging to the same species. The cited patent teaches that enzymatic treatment is intended to release cell surface molecules and that proteases including chymopapain and papain release cell surface proteins and glycoprotein antigens. The cited patent is considered to anticipate the claimed invention because it comprises identical active steps and, thus, the intended effects are reasonably expected to be identical as related to removal of antigens of MHC class I and to inhibition of donor tissue rejection, particularly in view that the cited patent demonstrates the better survival of animals received engraftment of enzymatically treated cells.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-9, 12-14 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,081,030 (Civin) taken with Galati et al (Cytometry. 1997, 27: 77-83), US 5,670,358 (Lee et al) and US 6,156,306 (Brownlee et al).

Claims are directed to a method for inhibiting rejection by a host mammal of a donor tissue transplant derived from another mammal wherein the method comprises step of treating a viable donor tissue with an enzyme effective for removing MHC Class I antigen and steps of transplanting and maintaining the treated viable tissue into/in the host mammal. Some claims are/are further drawn to the second transplanting step in the method for inhibiting transplant rejection. Some claims are further drawn to donor and host mammals belonging to the same or different species. Some claims are further drawn to host mammal being human. Some claims are further drawn to the use of tissues cells and/or organ parts such as blood cells, precursor cell, bone marrow cells, liver, brain, pancreas, kidney, etc. Some claims are further drawn to the use of enzyme papain and to the use of specific time and concentration for papain treatment of the donor tissue in the method for inhibiting transplant rejection

US 5,081,030 (Civin) teaches a method for transplantation of donor tissue cells that are enzymatically treated in order to remove surface molecules or glycoprotein antigens and it demonstrates better survival of host animals that received engraftment of the enzymatically treated donor tissue cells. The disclosure relates to graft vs. host disease (GVHD) and, thus, to inhibition of rejection of donor tissue by host recipient (col. 1, lines 26-33) as encompassed by the presently claimed invention. The cited patent demonstrates that increase of grafting cell doses result in better survival of engraftment recipients and, thus, the cited US 5,081,030 suggests transplantation of additional or second donor tissues as encompassed by the present invention

(claim 12). US 5,081,030 also teaches that release of various antigenic cell surface molecules is achieved with proteases and glycosidase (col. 4, lines 58- 68).

In the particular example, the cited patent US 5,081,030 (Civin) describes the use of chymopapain for enzymatic treatment of the donor tissue before transplantation into the recipient host. However, it further teaches and suggests enzymatic treatment with proteases including chymopapain or papain in order to release cell surface proteins and glycoprotein antigens (col. 5, line 2). Although the cited patent US 5,081,030 is silent that the enzymatically removed glycoprotein antigens are the MHC class I antigens, it is known that the enzymes that are used in the method of US 5,081,0303 including papain remove MHC class I antigens as adequately demonstrated by Galati et al (see abstract).

In the particular example, the cited patent US 5,081,030 (Civin) describes enzymatic treatment of donor bone marrow tissue cells before transplantation into the recipient host. However, it also teaches and suggests the use of a variety of cells that would be suitable for enzymatic treatment and transplantation including bone marrow cells, lymphocytes and hormone-secreting cells (col. 4, lines 8-10) and, thus, it suggests enzymatic treatment of tissue cells derived from various organs and/or organ parts including pancreas, liver, kidney, brain and others as encompassed by the claimed invention. In addition, US 5,670,358 (Lee et al) is relied upon to demonstrate that hepatocytes and islets cells preparations intended for transplantation are prepared by enzymatic treatment with enzymes chymopapain or papain (abstract).

The cited US 5,081,030 (Civin) teaches and demonstrates the better survival of host animals that received engraftment of the enzymatically treated viable donor tissue cells but it is silent about re-expression of MHC class I antigens. However, US 6,156,306 (Brownlee et al)

demonstrates that cells treated with papain in order to remove MHC class I surface molecules remain viable, functional and they will re-express the MHC class I surface molecules (col. 16, lines 10-17).

The cited reference by Galati also teaches that MHC class molecules are expressed by all nucleated cells and the cited patent US 5,081,030 (Civin) describes enzymatic treatment of tissue as intended for transplantation derived from various animal species including mammalians and humans, thereby, suggesting transplantation between different species upon enzymatic removal of antigenic surface structures.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to practice the presently claimed invention drawn to transplantation of viable donor tissues treated with enzymes capable to remove antigenic glycoproteins belonging to MHC class I as it is taught and suggested by US 5,081,030 (Civin) with a reasonable expectation of success in inhibiting rejection by host mammal of donor tissue and improving host survival as demonstrated by US 5,081,030 (Civin) because enzymes used and suggested in the method of US 5,081,030 (Civin) are capable to remove antigenic surface molecules including antigenic glycoprotein MHC class I as adequately demonstrated and taught by Galati et al. and US 6,156,306. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. It is considered to be within the purview of one of ordinary skill in the art to adjust time and concentration of enzymes including papain for treating donor tissues and for removal of antigenic molecules.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Claims 1-14 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,081,030 (Civin) taken with Galati et al. (Cytometry. 1997, 27: 77-83); US 5,670,358 (Lee et al) and US 6,156,306 (Brownlee et al) as applied to claims 1-9, 12-14 and 16-23 above, and further in view of Stone et al. (Transplantation. 1998. 65 (12): 1577-1583).

Claims 1-9, 12-14 and 16-23 as explained above. Claims 10 and 11 are further drawn to the use of combination of papain and alpha-galactosidase in the method for inhibiting transplant rejection.

US 5,081,030 taken with Galati et al., US 6,156,306 and US 5,670,358 are relied upon as explained above.

In particular example, the cited patent US 5,081,030 (Civin) describes enzymatic treatment of donor tissue with one enzyme. However, it also teaches that release of various antigenic cell surface molecules is achieved with proteases and glycosidase (col. 4, lines 58- 68). Glycosidase such as or alpha-galactosidase is known to remove alpha-gal epitopes from xenografts and, thereby to alter immune response of host recipient.

For example: the reference by Stone et al. demonstrates that transplantation of xenografts treated with or alpha-galactosidase reduced inflammatory response of recipients (see abstract). The reference by Stone et al. discloses a method for inhibiting transplant wherein the method comprises step of treating donor tissue with galactosidase and step of transplanting the treated tissue in to host recipient and wherein the method results in a reduction of inflammatory reaction or immune response of recipient host (pages 1577-1578 at paragraphs "Methods" and "Conclusions").

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was to combine papain and alpha-galactosidase for removal of antigenic and/or inflammatory cell surface molecules in the method for graft transplantations as suggested for generic protease and glycosidase by US 5,081,030 with a reasonable expectation of success in inhibiting rejection and reducing inflammatory host response because papain and alpha-galactosidase have been known and used in the prior art method for graft preparation and transplantation as adequately demonstrated by all cited references combined with Stone et al. One of skill in the art would have been motivated to combine two types of enzymes protease and glycosidase for the expected benefit in removing variety of cell surface antigenic structures as suggested by US 5,081,030. One of skill in the art would have been motivated to combine papain and galactosidase for the expected benefit in removing various surface antigenic structures because papain and alpha-galactosidase have been taught and suggested as particularly useful enzymes for removal of antigenic cell surface structures that are the MHC class I glycoproteins and the gal-epitopes respectively. Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

(10) Response to Argument

Applicant's arguments filed 10/10/2006 have been fully considered but they are not persuasive.

I. With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 5,081,030 (Civin) applicant argues (pages 7-12) that the Civin' reference does not teach or it is incapable of teaching the recited steps and elements of the Applicant's claims including step of enzymatic removal of MHC Class I antigens and step of transplantation of enzymatically treated cells into a host before re-expression of MHC Class I antigens because the primary goal of the enzymatic treatment in the Civin' method is intended for selection of progenitor cells and for release of sorted cells from immunomagnetic microsphers.

The argument is not found convincing because Civin teaches that the cell suspension after enzymatic treatment is substantially free of receptor materials (for example: abstract) and that the enzyme degrades the cell surface ligand to which receptor is bound without substantially decreasing cell viability (for example: col. 4, lines 56-58). Moreover, the disclosure that chymopapain treatment does not produce detectable damage clearly points out that cells remain viable as required by the Applicant's claims. The cells are treated with identical enzymes as required by the claimed invention and, thus, the same surface structures including MHC Class I antigens are removed in the cited method as encompassed by the claims.

Applicant argues that the hematopoietic progenitor cells in the Civin procedure are immature cells that do not yet exhibit MHC Class I antigen complexes in their surfaces (brief on appeal page 9, last par.) and, thus, the Civin teaching cannot be interpreted and/or it is incapable of teaching "temporarily ablating MHC Class I antigens" as recited in claim 1. The references by Itescu and by Gabbianelli that are cited by Applicant for support of arguments have been fully considered but they are not found to provide any persuasive grounds because they relate to the embryonic stem cells. The Civin patent discloses the use of adult tissues but not embryonic stem

cells. Moreover, with regard to the adult tissue-derived cells the reference by S. Itescu teaches that adult bone marrow derived cells express HLA (MHC) class I molecules (see it. 4). However, most importantly is the fact about Class I molecules being expressed on virtually all nucleated cells is a common knowledge to the person of ordinary skill in the art of immunology as evidenced by textbook by Abbas et al. "Cellular and Molecular Immunology" at page 78, at col. 1. The reference by Galati that is cited in the office action(s) also teaches that MHC class I molecules are integral membrane glycoproteins expressed on most nucleated cells (page 77, col. 1, par. 2). Thus, the sorted hematopoietic progenitor cells as being nucleated cells of adult tissue exhibit MHC Class I antigen complexes in their surfaces before enzymatic treatment in the method of the Civin's patent and the step of enzymatic treatment results in temporal removal or "ablating MHC Class I antigens" from the donor tissue in the Civin's method as encompassed by the applicants invention within the meaning of the instant claims and as it would be understood by the person of ordinary skill in the art of immunology.

Moreover, in one of the particular examples, the cited US 5,081,030 discloses a method for transplantation unsorted or whole bone marrow cells wherein the method comprises step of treating a viable donor tissue such as a whole bone marrow cell preparation with enzyme chymopapain (col.11, lines 30-35), step of transplanting the treated viable donor tissue into host mammal (col.11, line 45) and step maintaining the treated viable donor tissue in the host mammal (col. 11, line 57). The viable, enzyme-treated cells are reasonably expected to be capable to restore their biological structures and functions under conditions that that would maintain viability, grow and development of cells such as upon transplantation, for example. The viable cells are transplanted into host after enzymatic treatment. Thus, the cited method

comprises step of transplantation of enzymatically treated cells into a host before re-expression of antigens including before re-expression of MHC Class I antigens within the meaning of the claims.

1-9, 12-14 and 16-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,081,030 (Civin) taken with Galati et al. (IDS reference; Cytometry. 1997, 27: 77-83); US 5,670,358 (Lee et al) and US 6,156,306 (Brownlee et al).

II. With regard to the rejection of claims 1-9, 12-14 and 16-23 under 35 USC § 103 Applicant argue that the combination of cited references US 5,081,030 (Civin) taken with Galati et al., US 5,670,358 (Lee et al) and US 6,156,306 (Brownlee et al) does not render the claimed matter obvious because the Civin's method is unrelated to the claimed invention and the other references do not provide suggestion and reasonable expectation of success (brief on appeal pages 12-18).

Applicant argues that the Civin's patent (US 5,081,030) is unrelated because it cannot recognize removal of MHC Class I antigens from bone marrow cells since (accordingly to the applicant's arguments) the sorted immature cells do to express MHC Class I. However, the Civin's cell preparations are derived from adult tissue not embryonic tissue and, therefore, they express MHC Class I antigens at least to some degree as all adult nucleated cells. The Civin's patent clearly discloses removal of cell surface antigens with enzyme protease including chymopapain and papain (col. 5, line 2) and the enzymes that are used in the method of US 5,081,0303 remove the MHC class I antigens as adequately demonstrated by the cited reference by Galati et al (see abstract). Therefore, the combination of the cited references teach and/or

suggests the removal of antigenic structures including MHC Class I molecules and the combination of the cited references provides a reasonable expectation of success in inhibiting rejection by host mammal of donor tissue due to removal of antigenic structures including MHC Class I molecules.

As related to the Lee patent (US 5,670,358) Applicant argues that it teaches away since it teaches a method for inhibiting enzymatic effects on cells. However, the inhibition of enzymatic effects as taught by US'358 is intended to avoid excessive tissue digestion (col. 2, line 33) after enzymatic treatment or after enzymatic applications. In the office action, US 5,670,358 is relied upon to demonstrate that the presently claimed hepatocytes and islets cells useful for transplantation are prepared by enzymatic treatment with chymopapain or papain (abstract) in addition to a variety of cells that would be suitable for enzymatic treatment and transplantation taught and/or suggested in the Civin's patent.

As related to US 6,156,306 (Brownlee et al.) Applicant argues that if fails to suggest "temporarily ablating" MHC Class I antigens from donor tissue because it is primary concerned with permanent effect resulting from cell transfection. However, the cited patent US 6,156,306 was/is relied upon to demonstrate that the cells treated with papain (but not transfected, for example: see col. 16, line 15) re-express the MHC class I surface molecules (col. 16, lines 10-17).

Thus, the cited references in combination teach and suggests enzymatic treatment of cells and tissue transplants and they provide a reasonable expectation of success in inhibiting rejection by host mammal of donor tissue due to enzymatic removal of antigenic structures including MHC Class I molecules.

Applicant also argue that the cited references do not suggests some elements of the instant claims 12-14 and 16-20 that is step d) of transplanting a second donor (brief on appeal pages18-19). Applicants argue that the second transplantation relates to pre-tolerization as disclosed for the applicant's method. Yet, the term and/or concept of "pre-tolerization" as argued is not within the claimed subject matter. The cited prior art, for example: US 5,081,030 (Civin) demonstrates that increase of grafting cell doses result in better survival of engraftment recipients and, thus, the cited US 5,081,030 suggests transplantation of additional or second donor tissues as encompassed by the present invention (claim 12). Thus, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "pre-tolerization" by additional transplantation) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

III. With regard to the rejection of claims 1-14 and 16-23 under 35 U.S.C. 103(a) as being unpatentable over US 5,081,030 (Civin) taken with Galati et al., US 5,670,358 (Lee et al) and US 6,156,306 (Brownlee et al) and further in view of Stone et al. (brief on appeal pages 19-21) applicant argument are directed to the cited reference by Stone. Applicant argues that the enzymatic treatment of graft tissues as disclosed by Stone includes the use of lethal agents such as ethanol that would cause death of graft cells. However, alcohol is an additional agent. The reference by Stone et al. is mainly relied upon for the teaching that glycosidase such as or alpha-

galactosidase is known to remove alpha-gal epitopes from xenograft tissues in order to alter or to reduce immune response of host recipient upon transplantation.

Thus, the cited prior art combination teaches and/or suggests all critical limitations of the presently claimed method. Therefore, the claims are properly rejected under 35 USC § 103.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Vera Afremova,

Primary examiner AU 1657

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